DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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December 2, 2015

MEDOVENT GmbH
Dr. Thomas Freier
CEO
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Re: K143711
Trade/Device Name: Reaxon® Plus
Regulation Number: 21 CFR 882.5275
Regulation Name: Nerve Cuff
Regulatory Class: Class II
Product Code: JXI
Dated: October 29, 2015
Received: November 2, 2015

Dear Dr. Freier:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Carlos L. Pena -S

Carlos L. Peña, PhD, MS
Director
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Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K143711

Device Name
Reaxon® Plus

Indications for Use *(Describe)*

Reaxon® Plus is indicated for repair of peripheral nerve discontinuities up to 10 mm and where gap closure can be achieved by flexion of the extremity.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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B. Date Prepared: Oct/16/2015

C. Contact Person:

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D. Product Name: Reaxon® Plus

E. Common Name: Nerve Guide

F. Classification number/name: 21 CFR 882.5275 / Nerve Cuff

G. Product Code: JXI

H. Device description:

Reaxon® Plus is a flexible and transparent chitosan based implant designed for repair of peripheral nerve discontinuities up to 10mm and where gap closure can be achieved by flexion of the extremity.

Reaxon® Plus was developed to provide a protective environment for axonal growth across a nerve gap. When hydrated, Reaxon® Plus is an easy to handle, soft, pliable, transparent chitosan tube. Reaxon® Plus is provided sterile, non-pyrogenic, for single use in double blister packages in a variety of sizes as shown below.

Item number	RP321	RP330	RP340	RP350	RP360
Inner diameter (mm)	2.1	3.0	4.0	5.0	6.0
Length (mm)	30	30	30	30	30
Schematics of the ID (mm) of each size					
Real picture of each model of Reaxon® Plus.					

I. Intended Use:

Under supervision of a healthcare professional

- Reaxon® Plus is indicated for repair of peripheral nerve discontinuities up to 10 mm and where gap closure can be achieved by flexion of the extremity.

J. Predicate Device:

Reaxon® Plus is substantially equivalent in function and intended use to:

- NeuraGen® Nerve Guide, which is a tubular device designed for repair of peripheral nerve discontinuities. Like the predicate device, Reaxon® Plus is provided sterile, for single use only. Reaxon® Plus and NeuraGen® Nerve Guide are both manufactured from bioresorbable materials. Reaxon® Plus meets ISO 10993 requirements for biocompatibility.

A table of comparative features may be found below.

Parameter	Device	Predicate Device
Device name	Reaxon® Plus	NeuraGen® Nerve Guide
Company Name	Medovent GmbH	Integra LifeSciences Corporation
510(k) #	K143711	K011168
Material	Chitosan	Collagen
Indications For Use	Repair of peripheral nerve discontinuities up to 10 mm and where gap closure can	Repair of peripheral nerve discontinuities and where gap closure can be achieved

	be achieved by flexion of the extremity.	by flexion of the extremity.
Packaging	Double blister	Double blister
Sterilization Method	EO	EO

As indicated in the table of comparative features above, the difference between Reaxon® Plus and the predicate device is the material. As Reaxon® Plus is based on chitosan, the predicate device is based on collagen. Both chitosan and collagen are natural, animal-derived polymers that are biocompatible and biodegradable. In both Reaxon® Plus and the predicate device, the material is processed into sterile tubular nerve guides.

Given the difference between Reaxon® Plus and the predicate device, in vitro and in vivo biocompatibility testing according to ISO 10993 standards, long term implantation and bench tests on Reaxon® Plus have been performed to be used to establish substantial equivalence. These tests proved that Reaxon® Plus has a similar safety and effectiveness as its predicate device NeuraGen® Nerve guide.

Below there is a summary of each study that was performed.

Cytotoxicity

Purpose: To evaluate *in vitro* the cytotoxicity potential of Reaxon® Plus.

Method: A single preparation of the test article was extracted in single strength Minimum Essential Medium (IX MEM) at 37°C for 24 hours. Triplicate monolayers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% CO_2 for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration.

Result: No cytotoxicity. No evidence of cell lysis or toxicity. The test article extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity).

Acute systemic toxicity

Purpose: To evaluate for acute systemic toxicity in mice.

Method: A single dose of the extract of the test article was injected into a group of five animals, which were observed for signs of systemic toxicity immediately after injection and at 4, 24, 48 and 72 hours after injection. Body weights were recorded prior to dosing and on days 1, 2 and 3.

Result: There was no mortality or evidence of systemic toxicity from the extracts injected into mice. Each test article extract met the requirements of the study.

Sensitization

Purpose: to evaluate the potential of the test article to cause delayed dermal contact sensitization in the guinea pig maximization test.

Method: The test article was extracted in 0.9% sodium chloride USP and sesame oil, NF. Each extract was intradermally injected and occlusively patched to ten test guinea pigs (per extract).The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs (per vehicle). Following a recovery period, the test and control animals received a challenge patch of the appropriate test article extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal.

Result: The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test.

Irritation/Intracutaneous reactivity

Purpose: To evaluate for the potential to cause irritation following intracutaneous injection in rabbits.

Method: A 0.2 mL dose of the appropriate test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three animals. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection.

Result: No irritation. The test article met the requirements of the test since the difference between each test extract overall mean score and corresponding control overall mean score was 0.0 and 0.2 for the Sodium chloride and Sesame Oil test extracts, respectively.

Subacute toxicity

Purpose: The test articles were surgically implanted in rats to evaluate the potential systemic toxicity and local tissues response at the implantation site.

Method: Animals were observed for overt signs of toxicity. Detailed clinical examinations were conducted at pretreatment, weekly and at termination. A microscopic evaluation of the implantation sites and collected organs was conducted.

Result: No subacute toxicity. There was no evidence of systemic toxicity from the test article following subcutaneous implantation in the rat. The test article was classified as non-irritant as compared to the control article.

Implantation

Purpose: To evaluate the local tissue response of the test article implanted in muscle tissue of the rabbit.

Method: The test article and negative control were intramuscularly implanted and animals were euthanized 12 weeks later. Muscle tissues were excised and the implant sites examined macroscopically. A microscopic evaluation of representative implant sites from each animal was conducted to further define any tissue response.

Result: The macroscopic reaction was not significant as compared to the negative control article. Microscopically, the test article was classified as a non-irritant as compared to the negative control article.

Pyrogenicity

Purpose: To evaluated in the rabbit the potential for material mediated pyrogenicity.

Method: A single dose of 10 mL/kg was intravenously injected via the marginal ear vein into each of three animals. Rectal temperatures were measured and recorded prior to injection and at 30 minute intervals between 1 and 3 hours after injection.

Result: Non-pyrogenic. The total rise of rabbit temperatures during the 3 hour observation period was within acceptable USP limits. The test article was judged as non-pyrogenic.

Genotoxicity

Bacterial Reverse Mutation Study

Purpose: To evaluate whether a test article extract would cause mutagenic changes in *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* tester strain WP2uvrA in the presence and absence of mammalian metabolic activation.

Method: Tubes containing molten top agar were inoculated with culture from one of the five tester strains, along with the DMSO or saline extract. An aliquot of sterile water for injection or rat liver S9 homogenate, providing metabolic activation, was added. The mixture was poured across triplicate plates. Parallel testing was conducted with negative controls (extraction vehicle alone) and positive controls. The mean

number of revertants for the test extract plates was compared to the mean number of revertants of the negative control plates for each of the five tester strains.

Result: The DMSO and saline test article extracts were considered to be nonmutagenic to S. typhimurium tester strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* tester strain WP2uvrA.

Mouse Lymphoma Assay

Purpose: To evaluate whether the test article extract induced gene mutations and chromosomal damage in mammalian cells.

Method: The test article was soaked in sufficient volume (100 mL for the extraction in DMSO and 500 mL for the extraction in $RPMI_0$) of 0.9% sodium chloride (SC) to fully cover and submerge the sample. The test article was soaked for 10 minutes. The test article was removed from the saline, weighed, placed in a tightly capped vial, and delivered to the laboratory for immediate extraction. The test article and each of the negative controls (extraction vehicle without the test article) were subjected to the extraction. The $RPMI_0$ extract was supplemented to a 3% serum concentration prior to the 4 hour treatments and to a 10% serum concentration for the 24 hour treatment. The DMSO extract was diluted to a final concentration of 1.0% with $RPMI_3$ for the 4 hour treatments and with $RPMI_{10}$ for the 24 hour treatment. Each test extract and the negative control were tested in duplicate.

Result: The $RPMI_0$ and DMSO test article extracts did not cause a two-fold or greater increase in the mean mutant frequency of the L5178Y/$TK^{+/-}$ cell line either in the presence or absence of metabolic activation. The test article was not mutagenic.

Mouse Peripheral Blood Micronucleus Study

Purpose: To evaluate the potential for a test article extract to cause damage to chromosomes or the mitotic apparatus of murine erythroblasts by measuring the frequency of micronucleated reticulocytes (MN-RETs) in mice. Erythroblasts are erythrocyte precursor cells in the bone marrow.

Method: The test article was soaked in a sufficient volume (90 mL) of 0.9% sodium chloride (SC) to fully cover and submerge the sample. The test article was soaked for 10 minutes. The test article was removed from the saline, weighed, placed in a tightly capped vial, and delivered to the laboratory for immediate extraction. Twenty two or twenty three test articles were used for each extraction. The test article was subjected to the following extraction conditions: 50°C for 72 hours. The extracts were

continuously agitated during extraction. Fresh extracts were prepared for each day of dosing.

For three consecutive days, twelve mice per test article extract (six per sex) were injected intraperitoneally with the test article extracts. Similarly, six animals per sex were dosed with either the appropriate vehicle as the negative control or methyl methanesulfonate as a positive control. All animals were observed immediately following dosing and daily for assessment of general health. On day 4, blood was collected from the tail veins and reticulocytes were evaluated for the presence of micronuclei by flow cytometry.

Result: The test article extracts did not induce micronuclei in mice.

Long term implantation of Reaxon® Plus

Purpose: To evaluate the long term stability and tolerance of the implanted Reaxon® Plus.

Method: Reaxon® Plus was implanted in Wistar rats in a 10 mm rat sciatic nerve defect. After different implantation times (12, 24, 50 and 74/77 weeks) Reaxon® Nerve Guide was explanted and properties of the tubes, the connective tissue as well as the nerve cable analyzed to evaluate tissue reactions and the stability of the implanted nerve guide.

Results: The study demonstrated a slow degradation process and very mild tissue response after implantation of Reaxon® Plus. The analysis revealed a low number of activated macrophages at the implantation site of Reaxon® Plus showing low degradation activity in the chitosan tubes with good stability and only marginal signs of degradation until 50 weeks and first significant macroscopic signs of degradation at time point 74/77 weeks. The biological tissue response to Reaxon® Plus was found to be stable already at 3 months post-implantation, confirmed by the small and further decreasing number of macrophages and thickness of the fibrotic layer at the site of implantation which are indicators for a very mild tissue response.

Based on the results presented above we conclude that Reaxon® Plus has a similar safety as its predicate device NeuraGen® Nerve Guide.

Performance Characteristics

The mechanical and physical characteristics (bench tests) of Reaxon® Plus were evaluated in a series of tests. These tests were conducted to ensure that Reaxon® Plus possess the mechanical properties (suture retention and mechanical compression) as well as physical properties required for use in the human body. Testing has

demonstrated that the nerve guide is able to hold a suture and resist repeated compression from surrounding tissues.

These tests were done in direct comparison between Reaxon® Plus and its predicate device NeuraGen® Nerve Guide.

Dimensional / visual inspection

Purpose: To evaluate the influence of ethylene oxide sterilization on the dimensions of Reaxon® Plus.

Method: Direct measurement of the dimensions of the tubes before and after sterilization.

Result: Dimensional analysis was completed to verify that the dimensions of the Reaxon® Plus were within specified tolerances following ethylene oxide sterilization.

Suture retention strength test

Purpose: To evaluate the suture retention strength of the Reaxon® Plus.

Method: After 24 hours in PBS (pH 7.4) at RT, the tubes were incubated for 1 hour at 37°C for the measurement of suture retention. One extremity of the tube was clamped at the lower clamp of the mechanical tester. A suture thread (USP 6/0 Prolene) was used to pierce the tube at 2 mm from the top extremity (in both sides of the extremity). The suture was clamped at the top clamp of the mechanical tester. The force required to pull out the thread at constant cross-head speed at 1mm/min was monitored.

Result: Suture retention strength testing was completed to verify that Reaxon® Plus has sufficient strength to resist suture pull-out under loads exceeding those anticipated in the intended use environment.

Compression and Rebound analysis

Purpose: To evaluate the compression and rebound properties of Reaxon® Plus.

Method: A transverse compression test was performed. After incubating the tubes for 1 h at 37°C, 1 cm of each tube was tested. A displacement perpendicular to the longitudinal axis of the conduit was applied at a crosshead speed of 1 mm/min to a final displacement of approximately 60 % of the diameter of the conduits. The force “F” versus displacement “d” is recorded.

Result: Compression and rebound analysis was completed to verify that the Reaxon® Plus can withstand compressive forces greater than 0.25 N and it will re-open following removal of compressive forces sufficient to collapse the nerve guide.

K. Conclusion:

Reaxon® Plus is intended for use in repair of peripheral nerve discontinuities up to 10mm and where gap closure can be achieved by flexion of the extremity.

Reaxon® Plus is flexible to accommodate movement of joint while retaining its shape and it is resistant to occlusive forces from surrounding tissue.

Reaxon® Plus has sufficient strength to resist suture pull-out under loads exceeding those anticipated in the intended use environment.

Biocompatibility studies have demonstrated Reaxon® Plus to be non-cytotoxic, non-sensitizing, non-toxic, non-pyrogenic and non-genotoxic.

Based on the results of animal studies, in *vitro* product characterization studies, and in *vitro* and in *vivo* biocompatibility studies, we conclude that Reaxon® Plus has a similar safety and effectiveness profile as its predicate device NeuraGen® Nerve Guide.